REMARKS

I. Status Summary

Claims 1-27 and 46-53 are pending in the present U.S. patent application and have been examined.

Claims 1-10, 15, 19-27, and 46-53 have been rejected under 35 U.S.C. § 102(b) as being anticipated by Diehl *et al.* (1997) *Proc. Natl. Acad. Sci. USA* 94:5231-5236 (hereinafter "Diehl").

Claims 1-4 have been rejected under 35 U.S.C. § 102(b) as being anticipated by Bellamy *et al.* (1991) *Human Genetics* 87:341-347 (hereinafter "Bellamy").

Claims 11-14 and 16-18 have been rejected under 35 U.S.C. § 103(a) as being obvious over Diehl in view of Dindzans *et al.* (1986) *J. Immunol* 137:2355-2360 (hereinafter "Dindzans").

Reconsideration of the application based on the remarks set forth below is respectfully requested.

II. The Presently Disclosed Subject Matter

The presently disclosed subject matter pertains to a novel population of genetically diverse individuals that can be used for genetic mapping, methods for generating the disclosed population, and methods for using the disclosed population for efficient identification of genetic loci that modulate a phenotype. Also disclosed is an approach based upon a modification of basic recombinant inbred lines presently available, and as such represents an advance in the ability to use such lines for genetic mapping.

One aspect pertains to the creation of the population of genetically diverse individuals. Unlike recombinant inbred (RI) mouse lines, which are characterized by individuals that are genetically homogenous (*i.e.* each individual is homozygous for each locus/gene), the genetically diverse individuals of the presently disclosed subject matter are derived from these homogenous RI lines and are genetically diverse themselves.

Mice that make up a collection of RI lines are genetically diverse across the population (*i.e.* the RI panel), but are not genetically diverse individually. Each recombinant inbred intercross (RIX) individual of the presently disclosed subject matter thus has a complex genetic make-up, being homozygous at some loci and heterozygous at others. This is unlike the lines disclosed in Diehl, which employs basic RI lines that are made up of mice that individually are homozygous at each locus and thus not encompassed by the phrase "genetically diverse" as used in the instant application. The Diehl reference cited by the Patent Office does not use genetically diverse individuals, as Diehl discloses homozygous lines of mice that across all lines are genetically diverse but are not genetically diverse within a mouse, as no mouse disclosed in Diehl is heterozygous at any locus. As such, Diehl does not disclose a renewable population of genetically diverse individuals.

To more specifically point out the differences between the lines disclosed in Diehl and the presently disclosed subject matter, applicants submit **Exhibit A**. **Exhibit A** depicts a schematic showing the generation of recombinant inbred lines (RI) from two founder inbred lines, C57BL/6J and A/J (Note that this is the technique and the strains disclosed in Diehl). In **Exhibit A**, only two chromosome pairs are shown for simplicity, but it is understood that the two chromosome pairs represent all chromosomes of the mouse.

The initial step in the generation of a recombinant inbred line is the mating of two inbred lines, in this case C57BL/6J and A/J (*see* Step 1). This results in the production of an F1 generation, but as depicted in **Exhibit A**, each individual in the F1 generation is genetically identical: for each chromosome pair, one member of the pair will be a C57BL/6J chromosome (blue in **Exhibit A**) and one will be an A/J chromosome (yellow in **Exhibit A**). Thus, at the F1 generation, each mouse is genetically identical to every other mouse.

In order to produce a recombinant inbred line that can be used for genetic mapping, it is necessary to produce individual animals that are homozygous at each locus, while at the same time creating a population of animals that when taken together as a population show genetic diversity at the loci of interest. How

a recombinant inbred (RI) line is different from the recombinant inbred intercross (RIX) line disclosed in the subject patent application will be discussed in greater detail hereinbelow.

Returning to the production of an RI line from the F1 generation described above, members of the F1 generation (*i.e.* brothers and sisters) are mated to each other to produce an F2 (*see* Step 2). Animals in the F2 generation are heterozygous for at least a part of their genomes. This is depicted in **Exhibit A** as the presence of chromosome pairs where a region of one chromosome is blue and the corresponding region of the other chromosome is yellow (corresponding regions being depicted as horizontally directly across from each other in each side-by-side pair). It should be mentioned that the "mixing" of chromosomal segments that produces chromosomes with blue and yellow areas results from interchromosomal recombination.

Once an F2 generation is established, subsequent breedings are designed specifically to produce animals <u>that are homozygous at each locus</u>. This is conceded by the Patent Office on page 9 of the <u>Official Action</u>, wherein the <u>Dindzans</u> reference is quoted as teaching the importance of "a unique assortment of parental genes that are homozygous at every locus, as such strains are useful for the mapping of genes and restriction sites and in the elucidation of mechanisms of genetic control" (<u>Dindzans</u> at page 2355). This is accomplished by mating brothers and sisters for 20 generations. It is accepted in the field of mouse genetics (based upon statistical analysis) that after 20 generations of brother x sister matings each resultant mouse (now the F22 generation) will be homozygous at all loci. These matings are depicted in **Exhibit A** above as Steps 3-22.

After the 20 generations of brother x sister matings, recombinant inbred lines have been established. Each new inbred line is a unique mix of the two parental lines. Contrary to the Patent Office's assertions, however, this is not what is intended by the term "genetically diverse" as used in the instant patent application. The Patent Office appears to be interpreting "genetically diverse" as being equivalent to "having a different assortment of genes throughout the

genome", or alternatively, as "not genetically identical". Neither of these definitions is the meaning intended by applicants. As discussed herein, "genetically diverse" refers to an animal that displays heterozygosity at one or more loci. Within an RI line, all animals are genetically homogeneous (homozygous at all loci), and genetic heterogeneity at any particular locus can only be found by looking at different lines (*i.e.* horizontally across **Exhibit A**). Thus, an individual RI line cannot be used for genetic mapping, and it is only by analyzing multiple RI lines that mapping can be accomplished.

As such, a multiplicity of RI lines can be used for genetic mapping. However, the presently disclosed subject matter provides for greater precision in genetic mapping than can be achieved with RI lines. The generation of recombinant inbred intercross (RIX) lines entails going one very significant breeding step further than the generation of RI lines, and this step is completely antithetical to the strategy used to create the RI line. As stated hereinabove, RI lines are created by brother x sister matings in such a way as to generate homozygosis at every locus within an animal. RIX lines, on the other hand, are generated by crossing two distinct RI lines (*i.e.* two individuals that are not genetically identical; for example, by crossing a BXA1 male to a BXA2 female) to generate hybrid mice that are genetically diverse individually (*i.e.* not homozygous at each locus).

In summary, there are significant differences between the production of RI lines and RIX individuals. Each individual cross in an F2 generation can give rise to a unique RI line, and while the members of any given RI line will be genetically identical, the members of different lines will be genetically different. This genetic diversity among different RI lines makes it possible to do genetic mapping with RI lines. However, it must be reiterated that the goal of producing RI lines is to produce different lines of mice wherein each individual of each line is homozygous at every locus, but the different lines display genetic diversity when taken together. Put another way, an individual RI line does not comprise genetically diverse individuals, and it is only by looking at multiple RI lines that genetic diversity can be observed.

Another way to visualize this difference is to look horizontally across the RI lines and RIX individuals in **Exhibit A**. Compare the mouse depicted as BXA1 (a mouse from an RI line) to the mouse depicted as 1X2 (a mouse from an RIX line). Looking only at the first chromosome pair for each, one sees that the BXA1 mouse has the yellow (A/J) allele at the very top of each chromosome of the pair. Thus, at this locus the BXA1 mouse is not genetically diverse (*i.e.* it is homozygous at this locus). Consider next the 1X2 mouse. At the top of the first chromosome pair, this mouse has the yellow (A/J) allele on one chromosome of the pair and the blue (C57BL/6) allele on the other. This mouse is genetically diverse at this locus. One can see that the same is true for many different loci: each RI mouse individually will have either one allele or the other, but no RI mouse will have both. Thus, one of the major distinctions between a recombinant inbred (RI) line and a recombinant inbred intercross (RIX) individuals is that the former comprises only <u>non-genetically diverse individuals</u> and the latter comprises <u>genetically diverse individuals</u>.

Another aspect of the presently disclosed subject matter is the generation of RI lines from more than one (*e.g.* 3, 4, or 8) non-recombinant parent line. It should be noted that as used in the instant application, the generation of RI lines from more than one non-recombinant parent line is <u>not</u> equivalent to generating a mouse line from "multiple parents" as <u>Dindzans</u> is asserted to teach. For example, the generation of such RI lines from 4 non-recombinant parents is depicted in the schematic presented in **Exhibit B**.

Comparing **Exhibits A** and **B**, one notices that in **Exhibit B** an extra step occurs prior to the generation of the F1: namely, the breeding of two more non-recombinant inbred lines (in this case, C3H and DBA). The extra step of using 4 different non-recombinant inbred lines (instead of 2) results in a breeding pair chosen for the creation of the F1 that has more than two potential alleles at each locus. In **Exhibit B**, there are 4 potential alleles at each locus: the C57BL/6 allele, the A/J allele, the C3H allele, and the DBA allele. Thus, the RI lines can similarly have any one of four alleles at each locus. This is unlike the situation in <u>Dindzans</u>, in which each animal in the RI strain of <u>Dindzans</u> was (a) homozygous

at every locus; and (b) had either the C57BL/6 allele or the A/J allele at every locus. Thus, Dindzans does not teach the use of multiple (*i.e.* greater than 2) non-recombinant inbred strains to create the RI lines.

Continuing with the teaching of Dindzans, the Patent Office asserts that "multiple progenitors were used to establish their population for the expected benefit that using multiple progenitors creates a 'unique assortment of parental genes' which is 'useful for the mapping of genes and restriction sites and in the elucidation of mechanisms of genetic control'." Official Action at page 9. Applicants respectfully submit that this "unique assortment" is only true with reference to the genome of the animal as a whole and is not true with respect to individual loci within the animal. Dindzans' "unique assortment of parental genes" is strictly only true when one considers the whole mouse genome.

To demonstrate this point further, applicants offer the following example. Consider a trait that is controlled by more than one locus. For simplicity's sake, consider a trait controlled by two loci in the mouse. In this case, Dindzans' RI mouse can have only the following possible genotypes at any given loci P and Q: $P_{C57\text{-}C57}$ $Q_{C57\text{-}C57}$; $P_{C57\text{-}C57}$ $Q_{A/J\text{-}A/J}$; $P_{A/J\text{-}A/J}$ $Q_{C57\text{-}C57}$; and $P_{A/J\text{-}A/J}$ $Q_{A/J\text{-}A/J}$. In the population of RI lines all taken together, there will be mice with each of the stated genomes. There is a "unique assortment of parental genes" in a RI strain only because at P and Q the allele can be either C57 or A/J, but an individual mouse cannot have both at any locus (*i.e.* cannot be heterozygous at any locus). This limitation is not true in the case of an RIX strain of the presently disclosed subject matter. At each locus (in this example, P and Q), the RIX mouse will have (a) a choice from among the number of alleles that were present in the non-recombinant inbred lines that were used in the creation of the RI strains (*i.e.* 4 in **Exhibit B**); and (b) an individual RIX mouse can have more than one (*i.e.* it can be heterozygous at P, at Q, or at both P and Q). Thus, for an RI strain used to map a trait controlled by 2 loci, the number of potential genotypes is 2^2 or 4. For an RIX strain used to map a trait controlled by 2 loci, the number of potential genotypes is 2^n, where n is the number of non-recombinant inbred lines that were used in the creation of the F1 generation. In **Exhibit B**, there would be 16

different genotypes in the RIX line and only 4 in the RI strains (*i.e.* the strains Dindzans teaches).

In summary, applicants respectfully submit that Diehl does not disclose individuals that are genetically diverse as used in the instant application, and thus Diehl does not anticipate the presently disclosed subject matter. Additionally, the presently disclosed subject matter is not obvious in view of Diehl because the art of RI strain generation teaches away from the production of mice that are individually genetically diverse. And finally, Dindzans does not cure the defect in Diehl as Dindzans (a) does not teach genetically diverse individuals; and (b) does not teach generating RI strains from more than two non-recombinant inbred lines.

A second aspect of the instant invention is that the populations are renewable. By the population being "renewable", applicants intend that population that is being used for the genetic mapping must be reproducible such that new individuals that have the same genotypes can be produced simply.

There are two basic methods of producing a renewable population of genetically diverse individuals. The first is to clone an animal or a cell, for example, by growing a cell line. So long as the cell line has not been manipulated (*e.g.* become a recombinant cell line by the introduction of exogenous DNA), each daughter cell will be genetically identical to its progenitor.

The second method for creating a renewable population of genetically diverse individuals is to breed two or more inbred animals for one generation. Inbred animals by definition are not genetically diverse, meaning that they are homozygous at all loci. An example of an inbred line is any of the non-recombinant inbred mouse lines described above. Another example is a recombinant inbred (RI) line. Thus, for an RI line, each line can be maintained by breeding within the line because each "parent" will have the same genotype (*i.e.* the parents are genetically identical and are homozygous at each locus). For example, to generate more animals with the BXA1 genotype, it is only necessary to breed a male in the BXA1 line to a female in the BXA1 line. Since these animals are genetically identical at every locus, the pups born from this mating

will be genetically identical to their parents. This is the definition of an inbred line, and in this respect, the BXA1 line, for example, is an inbred line just as are its C57BL/6 and A/J ultimate grandparents.

The fact that inbred lines are homozygous at every locus provides the ability to generate a renewable population of genetically diverse individuals. If mice, for example, that are not inbred (*i.e.* are heterozygous at one or more loci) are used in the breeding, it is not possible to generate a renewable population because interchromosomal recombination between sister chromosomes during meiosis will "rearrange" the genome in a way that cannot be duplicated. Interchromosomal recombination events are random, and thus when a recombinant chromosome gets passed on to a progeny animal there is no way to produce a genetically identical animal again. When interchromosomal recombination occurs in an inbred line, on the other hand, the pieces of DNA that are exchanged in the recombination event are identical, and thus genetically it is as if the recombination event never occurred.

It is also possible to renew RIX lines. Looking at **Exhibit A**, a mouse in the RIX line depicted as "1X2" will have the exact same genotype as every other mouse that is created by breeding a mouse from the BXA1 line to a mouse from the BXA2 line. Thus, an RIX line is "a renewable population" because every animal that is born as a result of breeding BXA1 and BXA2 mice will be genetically identical to a 1X2 mouse. Additionally and as discussed hereinabove, an animal in an RIX line is genetically diverse because for each chromosome pair, the RIX mouse will carry one chromosome from BXA1 (for example) and one chromosome from BXA2 (for example). Since the BXA1 and BXA2 mice are not genetically identical, the 1X2 mouse will be heterozygous (*i.e.* genetically diverse) at each locus at which the BXA1 and BXA2 mice are different.

Summarily, RIX lines are renewable populations of genetically diverse individuals, and as such are different from the mice disclosed in Diehl and Dindzans. Diehl and Dindzans disclose renewable populations of genetically identical individuals that only display genetic diversity among different lines, not among individual members of the lines.

III. *Claim Rejections Under 35 U.S.C. § 102(b)*

III.A. *Claim Rejection in view of Diehl*

Claims 1-10, 15, 19-27, and 46-53 have been rejected under 35 U.S.C. § 102(b) as being anticipated by Diehl *et al.* (1997) *Proc. Natl. Acad. Sci. USA* 94:5231-5236 (hereinafter "Diehl"). The United States Patent and Trademark Office (hereinafter the "Patent Office") asserts that Diehl teaches a method for identifying multiple genetic loci (*Col2a1*, *Col1a1*, and *Col3a1*) that modulate a phenotype (facial clefting) in mice. According to the Patent Office, Diehl "performed a genome-wide search for loci contributing to susceptibility to teratogen-induced facial clefting in the mouse" using recombinant inbred (RI) mouse strains provided by M. Nesbitt. Official Action, page 2. The AXB and BXA RI lines are asserted to be crosses between A/J and C57BL6/J strains which were bred by intercrossing RI lines and maintained as a "renewable population of genetically diverse individuals". Diehl is also asserted to disclose the identification of loci using inbred lines using less than about 100 strains, identifying multiple genetic loci that modulate a phenotype, the modulation of a phenotype by a non-genetic factor (drug exposure), and the identification of an interaction among two or more non-genetic factors and a genetic locus.

After carefully considering the rejection and the Patent Office's asserted bases in support of the rejection, applicants respectfully traverse the rejection and offer the following remarks.

It is well settled that for a cited reference to qualify as prior art under 35 U.S.C. § 102, each element of the claimed invention must be disclosed within the reference. In re Bond, 910 F.2d 831, 15 U.S.P.Q.2d 1566 (Fed. Cir. 1990). "It is axiomatic that for prior art to anticipate under 102 it has to meet every element of the claimed invention." Hybritech Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 231 U.S.P.Q. 81 (Fed. Cir. 1986). When an alleged prior art reference does not disclose each an every element of the claimed invention, the claims cannot be rejected on the basis of anticipation. See, e.g., Atlas Powder Co. v. E. I. Du Pont de Nemours & Co., 750 F.2d 1569, 224 U.S.P.Q. 409 (Fed. Cir. 1984); Continental Can Co. U.S.A. Inc. v. Monsanto Co., 948 F.2d 124, 20 U.S.P.Q.2d

1746 (Fed. Cir. 1991). Upon careful consideration of Diehl, applicants respectfully submit that Diehl does not disclose each and every element of claims 1-10, 15, 19-27, and 46-53. Specifically, Diehl does not disclose a "renewable population of genetically diverse individuals" as that phrase is used in the present application.

Applicants respectfully submit that the phrase "genetically diverse" has been misinterpreted by the Patent Office, and when used as it is disclosed in the specification of the instant application and described hereinabove, it is clear that the mouse lines produced by Diehl, which are standard recombinant inbred lines, are not genetically diverse. According to the specification as filed, "a renewable population of genetically diverse individuals can comprise: (a) individuals produced by intercrossing recombinant inbred lines; (b) individuals produced by backcrossing recombinant inbred lines; (c) a cloned population of genetically diverse individuals; or (d) a panel of cell lines derived from genetically diverse individuals." The mouse lines that are disclosed in Diehl are not genetically diverse in this way. As noted above, the mouse lines disclosed in Diehl are all basic recombinant inbred lines, which do not fit the definition of "genetically diverse individuals" as used in the instant application.

Briefly, unlike the recombinant inbred lines of Diehl, a "genetically diverse" individual of the instant invention is itself (*i.e.* individually) genetically diverse (*i.e.* heterozygous at one or more loci), whereas the individuals of the RI strains of Diehl are not individually genetically diverse (*i.e.* are homozygous at all loci). As taught in the specification at page 6, lines 14-19, genetically diverse individuals can comprise individuals that result from intercrossing or backcrossing RI lines. The intercrossing or backcrossing step generates genetic diversity: *i.e.* heterozygosity at one or more loci. In contrast, an RI line is homozygous at all loci (*i.e.* not genetically diverse).

Applicants further submit that Diehl also does not teach the breeding of two different inbred lines to produce a renewable population of genetically diverse individuals. On the contrary, Diehl teaches the straightforward production of RI lines. According to the Patent Office, "AXB and BXA

recombinant inbred (RI) lines derived from crosses between A/J and C57BL6/J strains were supplied by M. Nesbitt and the mice were then bred by intercrossing recombinant inbred lines and maintained in a colony at the University of Michigan (page 5232) as a renewable population of genetically diverse individuals". Official Action at pages 6-7 (emphasis added). Applicants respectfully submit, however, that nowhere in Diehl does it state that mice were bred by intercrossing recombinant inbred lines. Rather, the cited passage states simply that "RI lines derived from crosses between A (A/J) and B (C57BL6/J) strains were supplied by M. Nesbitt (citation omitted). Mice were then bred (*i.e.* not intercrossed) and maintained in a colony at the University of Michigan". Diehl at page 5232. Applicants respectfully submit that "bred and maintained" is not equivalent to "bred by intercrossing recombinant inbred lines and maintained". In fact, as discussed in more detail hereinabove, until the disclosure provided in the applicants' specification, one breeding RI lines would not have intercrossed RI lines, because that would have destroyed the "unique assortment of parental genes that are homozygous at every locus [that are] useful for the mapping of genes and restriction sites and in the elucidation of mechanisms of genetic control" (Dindzans at page 2355; emphasis added). Undoubtedly, Diehl and co-workers would have desired to maintain the RI lines provided by Nesbitt. The only way to do so would be to perform brother x sister matings within each RI line, since only by breeding genetically identical animals could Diehl and co-workers be assured of maintaining their lines. This is not the same as an intercross or a backcross, in which genetically non-identical animals are bred together.

As such, applicants respectfully submit that the assertion that the RI mice in Diehl were "bred by intercrossing recombinant inbred lines" is not supported by the disclosure of Diehl. In fact, applicants respectfully submit that mouse geneticists working with RI lines would not intercross or backcross RI lines as this would destroy the homozygosity at each locus that is necessary for genetic mapping with RI strains. Put another way, an intercross or a backcross would introduce genetic diversity into an individual animal, and it is only within

applicants' specification that the use of genetically diverse individual animals for genetic mapping is disclosed.

The Patent Office has pointed out that "limitations in the specification and within applicants' remarks are not read into the claims as limitations of the instant claims under examination". Official Action at pages 4-5. In support of the rejection of claims 1-10, 15, 19-27, and 46-53 in view of Diehl, the Patent Office asserts the following:

> the claims as written do not require a specific amount of genetic diversity. Applicant should note that their definition of the recombinant inbred lines (ex. AXB and BXA) used in the Diehl et al. reference on page 12 of their specification; "refers to an inbred line derived from two unrelated inbred parent lines. An individual RI (ex. AXB or BXA) line has a characteristic combination of genes with a different pattern of alternative alleles at multiple loci". As a result, inherent in the recombinant inbred lines as defined by the applicant are "different patterns" and there an amount of genetic diversity that exists".

Official Action at page 5.

Having considered the Patent Office's assertion above, applicants respectfully submit that they are not attempting to impose limitations found in the specification on the claims. Applicants respectfully submit that as indicated hereinabove, the RI lines of Diehl are qualitatively different from the RIX individuals of the presently disclosed subject matter. Again, applicants submit that "a characteristic combination of genes with a different pattern of alternative alleles at multiple loci" does not amount to genetic diversity as used in the instant application. Applicants reiterate that to be "genetically diverse" as that term is used in the instant application, an individual must be heterozygous at at least one locus. Recombinant inbred strains do not qualify as genetically diverse under this definition. Put another way, genetic diversity is used in the context of individual loci in individual animals, not among loci in the same animal or among different animals. Animals that are homozygous at every locus are not genetically diverse as used in the instant application, even if unrelated loci are derived from different non-recombinant inbred lines.

Applicants respectfully submit that when considered in the context of how the phrase "genetically diverse" is being used in the present application, it becomes clear that the Diehl reference does not disclose a population of genetically diverse individuals. Thus, applicants respectfully submit that Diehl does not disclose each and every element of the claimed invention, and thus does not qualify as an anticipating reference under In re Bond, Hybritech, and Atlas Powder. Accordingly, applicants respectfully request that the rejection of claims 1-10, 15, 19-27, and 46-53 under 35 U.S.C. § 102(b) as being anticipated by Diehl be withdrawn. Applicants further respectfully submit that claims 1-10, 15, 19-27, and 46-53 are in condition for allowance, and respectfully request a Notice of Allowance to that effect.

III.B. Claim Rejection in view of Bellamy

Claims 1-4 are rejected under 35 U.S.C. § 102(b) as being anticipated by Bellamy *et al.* (1991) *Human Genetics* 87:341-347 (hereinafter "Bellamy"). According to the Patent Office, Bellamy teaches a method for identifying a genetic locus that modulates a phenotype comprising (a) providing a renewable population of diploid humans that are genetically diverse individuals; and (b) mapping the genomes of individuals within the renewable population of genetically diverse individuals that display the phenotype, whereby a genetic locus that modulates the phenotype is identified. Further, Bellamy is asserted to teach the above method wherein the renewable population comprises a panel of cell lines derived from the genetically diverse individuals.

After considering the rejection and the Patent Office's basis for the rejection, applicants respectfully traverse the rejection and submit the following.

Upon careful review of the Bellamy journal article, it becomes apparent that Bellamy fails to support an anticipation rejection of claim 1 of the instant application because Bellamy does not disclose each and every element of this claim. Bellamy discloses DNA fingerprinting as a method of determining relatedness among individuals, but does not teach how to use this information to map traits. Bellamy's teachings are limited to the generation of a pattern of

bands on a footprinting gel. Bellamy does not teach how to relate that information to the presence or absence of a particular trait in an individual, nor does it teach how to genetically map a trait using the information. In essence, Bellamy uses the cell lines strictly as a source of DNA, not as a tool for genetic mapping.

Furthermore, there is no discussion of relating the footprint to a particular phenotype. Even assuming *arguendo* that Figure 1 relates to a phenotype (although it only shows transmission of a phenotype in a large pedigree, but not how the footprint and phenotype are related), the authors do not discuss how the DNA fingerprinting method they describe can be used to genetically map a locus controlling the phenotype. Thus, applicants respectfully submit that Bellamy cannot be said to teach a method whereby a genetic locus that modulates a phenotype is identified.

Accordingly, applicants respectfully submit that Bellamy does not anticipate claim 1 of the instant patent application. Claims 2-4 depend from claim 1, and thus include all of the elements of claim 1. Accordingly, applicants respectfully submit that claims 2-4 have also been patentably distinguished from Bellamy. Applicants respectfully request that the rejection of claims 1-4 under 35 U.S.C. § 102(b) in view of Bellamy be withdrawn, and that the claims be allowed at this time.

IV. Claim Rejection Under 35 U.S.C. § 103

Claims 11-14 and 16-18 have been rejected under 35 U.S.C. § 103(a) as being obvious over Diehl in view of Dindzans *et al.* (1986) *J. Immunol* 137:2355-2360 (hereinafter "Dindzans"). The Patent Office asserts that Diehl teaches a method for identifying multiple genetic loci. The Patent Office concedes, however, that Diehl does not teach the derivation of the RI lines from at least 3, 4, or 8 non-recombinant parent lines. The Patent Office asserts that Dindzans teaches the production of RI lines from multiple parent strains. The Patent Office thus contends that it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have modified the identification of

a genetic locus that modulates a phenotype of Diehl so as to have included the diverse population of non-recombinant, parent lines derived from at least 3, 4, or 8 non-recombinant parent lines.

After carefully considering the rejection and the Patent Office's asserted bases in support of the rejection, applicants respectfully traverse the rejection and offer the following remarks.

Preliminarily, applicants note that the U.S. Court of Appeals for the Federal Circuit (C.A.F.C.) has set forth in Environmental Design Ltd. v. Union Oil Co., 713 F.2d 693 (Fed. Cir. 1983), cert. denied, 464 U.S. 1043 (1984), that the factual determinations to be made, as well as the evidence to consider, in making an obviousness determination under §103 include:

a) the scope and content of the prior art;
b) the differences between the prior art and the claimed invention;
c) the level of ordinary skill in the pertinent art; and
d) additional evidence, which may serve as indicia of non-obviousness.

All relevant evidence on each of these four dispositive issues must be fully considered and evaluated to determine whether the claimed invention would have been obvious. Additionally, it is well known that for an obviousness-type rejection to stand, the cited document or combination must disclose all aspects of the claimed invention; contain a suggestion to modify the cited document(s) to arrive at the claimed invention; and there must be a reasonable chance of success.

In Hodosh v. Block Drug Co., 786 F.2d 1136 (Fed. Cir. 1986), the U.S. Court of Appeals for the Federal Circuit set forth what is described as the "tenets of patent law that must be adhered to when applying §103", Id. at 1143, n.5. Those tenets set out in Hodosh are:

a) the claimed invention must be considered as a whole;
b) the references must be considered as a whole and suggest the desirability and thus obviousness of making the combination;
c) the references must be reviewed without benefit of hindsight vision

afforded by the claimed invention; and

d) "ought to be tried" is not the standard with which obviousness is determined.

The claims subject to the present rejection depend from claims 1 and 2. Claim 1 recites a method for identifying a genetic locus that modulates a phenotype comprising: (a) providing a renewable population of genetically diverse individuals; and (b) mapping the genomes of individuals within the renewable population of genetically diverse individuals that display the phenotype, whereby a genetic locus that modulates the phenotype is identified.

Claim 2 depends from claim 1, and recites that the renewable population of genetically diverse individuals comprises: (a) individuals produced by intercrossing recombinant inbred lines; (b) individuals produced by backcrossing recombinant inbred lines; (c) a cloned population of genetically diverse individuals; or (d) a panel of cell lines derived from genetically diverse individuals.

Claims 11-14 and 16-18 then recite that the recombinant inbred lines comprise recombinant inbred lines derived from at least 3 (claims 11 and 16), 4 (claims 12 and 17), or 8 (claims 13 and 18) non-recombinant parent lines. Claim 14 depends from claim 11, and recites that the at least three non-recombinant parent lines comprise one or more non-recombinant parent lines selected from the group consisting of mouse lines C57BL/6, BALB/c, C3H, A, 129, and DBA/2.

Applicants respectfully direct the Patent Office's attention to the deficiencies of the Diehl reference discussed hereinabove. Diehl does not teach the derivation of the RI lines from at least 3, 4, or 8 non-recombinant parent lines. However, contrary to the Patent Office's contentions, applicants respectfully submit that the Dindzans reference does not disclose the production of RI lines from multiple (*i.e.* 3 or more) non-recombinant parental lines. As recited on page 2356 of Dindzans, "RI strains were derived by inbreeding mice from the F_2 generation of the cross between A/J (A) and C57BL/6J (B) mice".

The Patent Office contends that Dindzans teaches the production of RI lines from multiple parent strains. Applicants respectfully submit that this is not the same a producing RI or RIX lines from multiple non-recombinant parental

lines. Applicants respectfully point out that Dindzans only used 2 non-recombinant parental lines: A/J and C57BL/6J, not the at least 3 recited in claims 11-14 and 16-18 of the instant application. This point is explicitly conceded by the Patent Office on page 9 of the Official Action, wherein it is stated "Dindzans et al. do not teach the derivation of the RI lines from at least 3, 4, or 8 non-recombinant lines". As such, applicants respectfully submit that the combination of Diehl and Dindzans does not disclose each and every element of the claimed invention, and thus, a prima facie case of obviousness has not been established.

The Patent Office then cites Hedrich (1981) Genetic Monitoring, Chapter 8 in The Mouse in Biomedical Research, volume I (hereinafter "Hedrich"). The Patent Office asserts that Hedrich:

> teaches the organization of breeding colonies from a founding colony made up of 8-10 breeding pairs. Hedrich teaches in his Chapter on "genetic monitoring" of the mouse in biomedical research that the organization of breeding colonies should include propagation steps consisting of three groups: "foundation colony (FC), pedigreed expansion colony (PEC), and production colonies (PC)". Hedrich further teaches that the "foundation colony, which preserves the germline, should be of limited size" and that it may either be built up as a single line (SL) or in a modified parallel line (MPL) system. With the SL system, Hedrich teaches that "SL colony members are usually more closely related to each other". In contrast, Hedrich teaches that "in the MPL system e.g. three family lines are kept for four generations, each consisting of not more than 8-10 breeding pairs". The reference continues to teach that "one breeding pair of the foundation colony is selected as common ancestor, whose offspring will again give rise to three family lines" and further that "the degree of kinship is varying from generation to generation within the cycle". The reference teaches that this method makes "it possible to select among the lines that one which matches the original standards best".

Official Action at page 10.

From this, the Patent Office asserts:

> it would have prima facie obvious to one of ordinary skill in the art at the time the invention was made to have modified the identification of a genetic locus that modulates the phenotype of Diehl et al. so as to have included the diverse population of non-recombinant, parent lines of Dindzans et al. and to have derived their breeding population from at least 3, 4, or 8 non-recombinant parent lines as taught in further view of Hedrich, not only for the expected benefit that more parents would obviously result in more diverse progeny, but also for the expected benefit of providing additional means for furthered variation among mouse lines and for the ability taught by Hedrich of making "it possible to select among the lines that one which matches the original standards best".

Official Action at pages 10-11.

Initially, applicants respectfully traverse the Patent Office's assertions reproduced immediately above. Applicants respectfully submit that contrary to the Patent Office's assertions, Dindzans does not disclose a "diverse population of non-recombinant parent lines". On the contrary, Dindzans employed only two non-recombinant parent lines as discussed in more detail hereinabove: C57BL/6 and A/J. The Patent Office appears to be suggesting that the F1 generation of the cross between C57BL/6 and A/J (*see* Step 1 of **Exhibit A**), or perhaps one of the mouse lines produced in Steps 2-22 of **Exhibit A**, produces a non-recombinant parent. This is not the case. Once the F1 generation is formed by crossing two non-recombinant inbred lines, a recombinant hybrid mouse is produced in the F1, and even after twenty generations of breeding to produce an RI strain are performed, the resulting mouse remains a recombinant inbred mouse. The only non-recombinant mouse lines disclosed by Dindzans are C57BL/6 and A/J. Thus, contrary to the Patent Office's assertions, Dindzans does not teach the use of at least 3, 4, or 8 non-recombinant parent lines as recited in claims 11 and 16, 12 and 17, and 13 and 18, respectively. With regard to claim 14, claim 14 depends from claim 11, and thus includes all of the elements of claim 11: in this case, the use of at least 3 non-recombinant parent lines.

This defect in Dindzans is not cured by consideration of Hedrich. Hedrich does not teach the use of more than 2 non-recombinant parent lines. Hedrich only teaches very basic strategies for setting up and maintaining a mouse colony. In particular, Hedrich teaches three groups of colonies that can be used to propagate an inbred strain. Again, the Patent Office appears to be misconstruing at which stage in the production of an RIX line the relevant "parents" are present. In either Schematics A or B, the only non-recombinant parents sit at the very top lines: C57BL/6, A/J, C3H, DBA, etc. Every breeding step between the initial breeding of a non-recombinant, inbred line and another non-recombinant, inbred line involves breeding recombinant (*i.e.* hybrid) mice.

The fact that Hedrich teaches the presence of "8-10 breeding pairs" is irrelevant, as Hedrich does not teach that these breeding pairs (a) are not identical to each other; and/or (b) are derived from more than 2 non-recombinant parent lines. Thus, Hedrich does not cure the defect present in Dindzans, and conceded by the Patent Office, that neither Diehl nor Dindzans teach the derivation of the RI lines from at least 3, 4, or 8 non-recombinant lines. These are elements that are recited in claims 11-14 and 16-18, and since the cited references do not teach or suggest these elements, a prima facie case of obviousness has not been established.

As a result, applicants respectfully submit that the combination of Diehl and Dindzans does not support the current rejection, even in view of Hedrich. Accordingly, applicants respectfully request that the rejection of claims 11-14 and 16-18 under 35 § 103(a) be withdrawn and the claims be allowed at this time.

CONCLUSIONS

In light of the above amendments and remarks, applicants submit that the application is in condition for allowance and courteously solicit a Notice of Allowance.

If any small matter should remain outstanding after the Patent Examiner has had an opportunity to review the above Remarks, the Patent Examiner is

respectfully requested to telephone the undersigned patent attorney in order to resolve these matters and avoid the issuance of another Official Action.

DEPOSIT ACCOUNT

The Commissioner is hereby authorized to charge any deficiencies of payment or credit any overpayments associated with the filing of this correspondence to Deposit Account No. **50-0426**.

Respectfully submitted,

JENKINS, WILSON & TAYLOR, P.A.

Date: 12/5/2003 By: ______________________

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421/34/2
AAT/CPP/ptw
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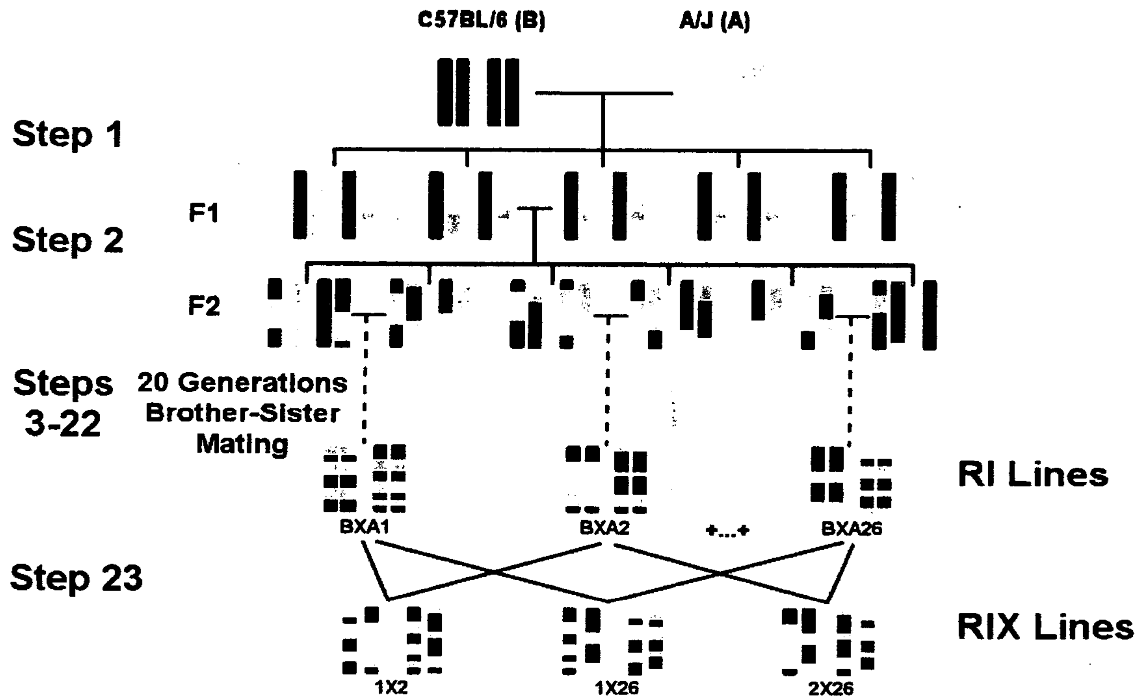
Enclosures

Serial No.: 09/998,058

EXHIBIT A



Serial No.: 09/998,058

EXHIBIT B